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Proposed Registration Decision

Cloransulam-methyl

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Table of Contents

Overview 1
- Proposed Registration Decision for Cloransulam-methyl 1
- What Does Health Canada Consider When Making a Registration Decision? 1
- What Is Cloransulam-methyl? 2
- Health Considerations 2
- Environmental Considerations 4
- Value Considerations 5
- Measures to Minimize Risk 5
- Next Steps 6
- Other Information 6

Science Evaluation 7

1.0 The Technical Grade Active Ingredient, Its Properties and Uses 7

2.0 Methods of Analysis 7

3.0 Impact on Human and Animal Health 7
- 3.1 Toxicology Summary 7
- 3.2 Determination of Acceptable Daily Intake 10
- 3.3 Acute Reference Dose 10
- 3.4 Occupational and Bystander Risk Assessment 10
- 3.5 Food Residues Exposure Assessment 11
  - 3.5.1 Residues in Plant and Animal Foodstuffs 11
  - 3.5.2 Dietary Risk Assessment 11
  - 3.5.3 Aggregate Exposure and Risk 11
  - 3.5.4 Established Maximum Residue Limits 11

4.0 Impact on the Environment 12
- 4.1 Fate and Behaviour in the Environment 12
- 4.2 Effects on Non-Target Species 13
  - 4.2.1 Effects on Terrestrial Organisms (Appendix I, Tables 8 and 10) 13
  - 4.2.2 Effects on Aquatic Organisms (Appendix I, Tables 9 and 11) 14

5.0 Value 15

6.0 Formulants and Microcontaminants of Health and Environmental Concern 15
- 6.1 Toxic Substances Management Policy Considerations 15
- 6.2 Formulants of Health Concern 16

7.0 Summary 16
7.1 Human Health and Safety 16
7.2 Environmental Risk 16
7.3 Value 17

8.0 Proposed Regulatory Decision 17

List of Abbreviations 19

Appendix I 21
Table 1 Summary Table of Toxicology Studies on Cloransulam-methyl (technical grade active ingredient) and FirstRate Herbicide Water Dispersible Granules (end-use product) 21
Table 2 Residue Analysis in Plant Products 29
Table 3 Integrated Food Residue Chemistry Summary 29
Table 4 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment 34
Table 5 Differences Between Canadian MRLs and Other Jurisdictions 35
Table 6 Fate and Behaviour in the Terrestrial Environment 35
Table 7 Fate and Behaviour in the Aquatic Environment 36
Table 8 Toxicity to Non-Target Terrestrial Organisms 37
Table 9 Toxicity to Non-Target Aquatic Organisms 38
Table 10 Screening Level Risk Assessment on Non-Target Species Risk to Terrestrial Organisms 40
Table 11 Screening Level Risk Assessment on Non-Target Species Risk to Aquatic Organisms 41

References 43

Overview

Proposed Registration Decision for Cloransulam-methyl

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing conversion from conditional to full registration for Cloransulam-methyl Technical Herbicide and the end-use product FirstRate Herbicide Water Dispersible Granules containing the technical grade active ingredient cloransulam-methyl to control specific broadleaf weeds in soybeans.

An evaluation of available scientific information found that, under the approved conditions of use, the end-use product has value and does not present an unacceptable risk to human health or the environment.

This overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Cloransulam-methyl Technical Herbicide and FirstRate Herbicide Water Dispersible Granules.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions or proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive human populations (e.g. children) as well as organisms in the environment (e.g. those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties present when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the PMRA's website at www.pmra-arla.gc.ca.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and c) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on cloransulam-methyl, the PMRA will consider all comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision document[4] on cloransulam-methyl, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation in this consultation document.

What Is Cloransulam-methyl?

Cloransulam-methyl is the active ingredient in the end-use product FirstRate Herbicide Water Dispersible Granules. FirstRate Herbicide Water Dispersible Granules may be applied as a pre-emergent herbicide, i.e. a herbicide applied before the crop has emerged above the ground, or as a postemergent herbicide, i.e. a herbicide applied after the crop has emerged above the ground. It is applied to soybeans in Eastern Canada using ground equipment to control specific broadleaf weeds. Cloransulam-methyl acts on the acetolactate synthase (ALS) enzyme in the target weeds. Sensitive seedlings stop growing and eventually die.

Health Considerations

Can Approved Uses of Cloransulam-methyl Affect Human Health?

Cloransulam-methyl is unlikely to affect your health when used according to the label directions.

Potential exposure to cloransulam-methyl may occur through diet (food and water) or when handling and applying the products. When assessing health risks, two key factors are considered: the levels at which no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (e.g. children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100 times higher (and often much higher) than levels to which humans are normally exposed when using cloransulam-methyl products according to the label directions.

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[3] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

[4] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

The technical grade active ingredient cloransulam-methyl and the end-use product FirstRate Herbicide Water Dispersible Granules did not exhibit any adverse effects in the acute studies. Cloransulam-methyl did not cause cancer in animals and was not genotoxic. There was no indication cloransulam-methyl caused damage to the nervous system and there were no effects on reproduction. The first signs of toxicity in animals given daily doses of cloransulam-methyl over longer periods of time were effects on the liver and kidneys. The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

When cloransulam-methyl was given to pregnant animals, no effects were observed on the developing fetus or young animals. This indicates that the fetus or young animals were not more sensitive than the mothers and specific protection is not required in the risk assessment.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Aggregate dietary risk estimates (food and water) revealed that the general population and infants, the segment of the population that would ingest the most cloransulam-methyl relative to body weight, are expected to be exposed to less than 0.4% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from cloransulam-methyl is not of concern for all population groups.

Animal studies revealed no acute health effects. Consequently, a single dose of cloransulam-methyl is not likely to cause acute health effects in the general population (including infants and children).

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Soybean residue trials using cloransulam-methyl conducted throughout the United States in zones representative of Canada were acceptable. The MRLs for dry soybean can be found in the Science Evaluation of this consultation document.

Workplace Risks From Handling FirstRate Herbicide Water Dispersible Granules

Occupational risks are not of concern when FirstRate Herbicide Water Dispersible Granules is used according to the label directions, which include protective measures.

The requested use for FirstRate Herbicide Water Dispersible Granules should not result in unacceptable risk to workers that mix/load/apply the product or to workers that enter treated areas. A risk assessment was conducted using the Pesticide Handler's Exposure Database (PHED) to quantify exposure to cloransulam-methyl while mixing, loading and applying FirstRate Herbicide Water Dispersible Granules.

Calculated margins of exposure (MOEs) for both farmers and custom applicators applying FirstRate Herbicide Water Dispersible Granules exceed the target margin of exposure and are not of concern.

As the product would be applied pre-emergence or postemergence, prior to the flowering stage of soybean, re-entry activities should be minimal. As such, exposure and risk to re-entry workers should be negligible.

Environmental Considerations

What Happens When Cloransulam-methyl Is Introduced Into The Environment?

Cloransulam-methyl is toxic to terrestrial and aquatic vascular plants as well as algae. Therefore, label instructions are required to protect these organisms when the product is applied. Buffer zones and other instructions on the product label are intended to protect the environment.

Cloransulam-methyl presents a negligible risk to honey bees, birds, wild mammals, earthworms, fish and crustaceans.

Cloransulam-methyl is introduced into the environment when used as a herbicide in soybeans. It is slightly persistent in soil and in water. Cloransulam-methyl has a low potential for significant carryover to the next growing season. Field data for broadcast spray application indicated there was no leaching of cloransulam-methyl in the soil. Neither cloransulam-methyl nor its major breakdown products are expected to enter groundwater. Cloransulam-methyl is not expected to enter the atmosphere.

Value Considerations

What Is the Value of FirstRate Herbicide?

FirstRate Herbicide Water Dispersible Granules is a pre-emergent or postemergent herbicide to control specific broadleaf weeds in soybeans.

A single application of FirstRate Herbicide Water Dispersible Granules provides effective control of specific broadleaf weeds in soybeans. FirstRate Herbicide Water Dispersible Granules is compatible with integrated weed management practices, conservation tillage and conventional crop production systems. As FirstRate Herbicide Water Dispersible Granules may be applied after weeds have emerged, producers can better assess whether this herbicide is necessary or suitable for the particular weed species present.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of FirstRate Herbicide Water Dispersible Granules to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

- **Human Health**

Applicators and other handlers must wear a long-sleeved shirt, long pants and chemical-resistant gloves.

- **Environment**

To reduce exposure of terrestrial plants, a buffer zone of 35 metres between the last spray swath and the edge of sensitive areas, such as shelterbelts and woodlots, is required. Similarly, to reduce exposure of aquatic vascular plants and algae, a buffer zone of seven metres between the last spray swath and the edge of sensitive aquatic systems, such as rivers, lakes, streams and ponds, is required.

Next Steps

Before making a final registration decision on the conversion of cloransulam-methyl from conditional to full registration, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision document, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

At the time the PMRA makes its final registration decision, it will publish a Registration Decision on cloransulam-methyl (based on the Science Evaluation in this consultation document and Regulatory Note REG2001-08, *Cloransulam-methyl*). In addition, only the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

1.0 The Technical Grade Active Ingredient, Its Properties and Uses

Refer to Regulatory Note REG2001-08, *Cloransulam-methyl*, for a detailed assessment of the chemical properties and use information of cloransulam-methyl and FirstRate Herbicide Water Dispersible Granules.

2.0 Methods of Analysis

Refer to REG2001-08 for a detailed assessment of the methods of analysis for cloransulam-methyl and FirstRate Herbicide Water Dispersible Granules.

3.0 Impact on Human and Animal Health

Refer to REG2001-08 for a detailed assessment of the impact on human and animal health of cloransulam-methyl and FirstRate Herbicide Water Dispersible Granules.

The required short-term toxicity studies and analytical methodologies for animal tissues, as presented in REG2001-08, have been submitted to the PMRA and have been found to be satisfactory.

3.1 Toxicology Summary

In rats, orally administered cloransulam-methyl is rapidly absorbed and eliminated. At single oral doses of 5 or 1000 mg/kg bw or repeat oral doses of 5 mg/kg bw/d for 15 days, the overall recovery of the administered dose in 72 hours in the excreta is over 90%. There are sexual differences in the metabolism of orally administered cloransulam-methyl. Female rats appear to eliminate orally administered cloransulam-methyl more efficiently, with half-lives of elimination of 6.5–7.9 hours, while those for males were 8–13.2 hours. With a single low dose of 5 mg/kg bw, urinary elimination predominated in female rats (68–80%), while fecal excretion accounted for only about 21%. For the males, elimination in the urine and feces was similar (41–52%). With a single high dose of 1000 mg/kg bw, elimination was mainly fecal, at 78%–83% in both male and female rats. Urinary excretion accounted for 10%–17% of the administered dose. Residues in tissues and the carcass were low, <5% of the administered doses and the highest levels were found in the blood, kidneys and liver (0.03–0.04% of administered dose/g tissue). Analyses of metabolite profiles revealed up to 11 and 8 peaks in the urine and feces, respectively. The metabolites identified were unchanged parent 4-OH-phenyl-XDE-565, OH-pyrimidine-XDE-565, XDE-565-7-N-acetylcysteine in the urine, and unchanged parent compound and 4-OH-phenyl-XDE-565 in the feces. The unchanged parent compound accounted for over 70% of the fecal metabolites in both male and female rats that were dosed with cloransulam-methyl at 1000 mg/kg bw. The unchanged parent compound also accounted for a high percentage (%) of the urinary metabolites in female rats given the low dose (5 mg/kg bw/d) of cloransulam-methyl, but accounted for only 22% of the urinary metabolites in the males.

Metabolism of cloransulam-methyl is similar after a single oral dose of 5 mg/kg bw or after 15 daily oral doses of 5 mg/kg bw/d.

Technical cloransulam-methyl is of low acute toxicity by the oral (rat), dermal (rabbit) and inhalation (rat) routes of exposure and the respective acute LD_{50} or LC_{50} are >5000 mg/kg bw, >2000 mg/kg bw and >3.77 mg/L (actual). When tested in rabbits, cloransulam-methyl was minimally irritating to the eye and not a skin irritant. The dermal sensitization potential of cloransulam-methyl could not be assessed due to a deficient study. However, the dermal sensitization data generated with the end-use formulation of cloransulam-methyl, FirstRate Herbicide Water Dispersible Granules, demonstrated the lack of dermal sensitization potential. Due to the high percentage (84%) of cloransulam-methyl in the formulated product, the data could be used to fill the deficient toxicological database of the technical active. It is therefore estimated that technical cloransulam-methyl is unlikely to be a dermal sensitizer.

FirstRate Herbicide Water Dispersible Granules is also of low acute toxicity by the oral (LD_{50} in rats > 5000 mg/kg bw) and dermal (LD_{50} in rabbits > 2000 mg/kg bw) routes of exposure. It was not an eye or skin irritant when tested in the rabbit, nor a dermal sensitizer when tested in the guinea pig. No acute inhalation toxicity data are available for FirstRate Herbicide Water Dispersible Granules. However, based on the high percentage of cloransulam-methyl in the formulation and no evidence of inhalation toxicity of other formulant ingredients in the formulation, the acute inhalation toxicity of FirstRate Herbicide Water Dispersible Granules is considered to be similar to that of the technical active, i.e. low acute inhalation toxicity. After 21 days of dermal exposure to FirstRate Herbicide Water Dispersible Granules at doses up to 1000 mg/kg bw/d in rabbits, the only treatment-related effect observed was anemia in the females at the highest dose tested. Treatment had no effects on mortality, clinical signs, food consumption, body weight, clinical chemistry, organ weight or gross histopathology.

Short-term toxicity data are available after dietary exposure to the mouse (90-day), rat (90-day rat and four-week recovery) and dog (two-week, 90-day and one-year), as well as to the rabbit after dermal exposure (21-day). In both the 90-day mouse and one-year dog studies, dietary exposure to cloransulam-methyl resulted in liver pathology and effects on a few clinical chemistry parameters that are related to liver pathology (e.g. higher serum levels of liver enzymes such as alkaline phosphatase and SGPT). Based on liver pathology, the LOAEL and NOAEL for male mice are 100 and 50 mg/kg bw/d, respectively, and those for female mice are 500 and 100 mg/kg bw/d, respectively. Also based on liver pathology, the LOAEL and NOAEL for male and female dogs are 10 and 5 mg/kg bw/d, respectively. In the 90-day and 4-week recovery rat study, the LOAEL is 100 mg/kg bw/d based on kidney effects (increased incidence of fatty vacuolation in the proximal tubules in females and hypertrophy of the collecting duct cells in males). The NOAEL was not determined. In the 90-day dog study, the LOAEL was 200 mg/kg bw/d, based on decreased body weight, body-weight gain, food consumption and red blood cell parameters, as well as altered organ weights (increased absolute and relative thyroid weights and decreased relative and absolute testes weights) and histopathology findings (hypertrophy and decreased colloid in the thyroid, and decreased spermatogenesis and degeneration of the epithelium of the seminiferous tubules of the testes). The NOAEL is 40 mg/kg bw/d. The findings of the 21-day dermal toxicity study of cloransulam-methyl in rabbits mimic those of the study with FirstRate Herbicide Water Dispersible Granules,

i.e. the only effect observed was anemia in female rabbits at the highest dose level tested (1000 mg/kg bw/d). Thus, the short-term dermal toxicity LOAEL and NOAEL for female rabbits are 1000 and 500 mg/kg bw/d, respectively, and the NOAEL for male rabbits is 1000 mg/kg bw/d, the highest dose level tested.

Long-term toxicity data in mice and rats did not demonstrate any oncogenic potential for cloransulam-methyl. The treatment-related toxic effects were perineal staining (rats), reduction in body weight and body-weight gain (male and female mice at 1000 mg/kg bw/d, female mice at 100 mg/kg bw/d, male and female rats at 325 mg/kg bw/d) and pathology of the liver, kidneys and possibly the thyroid. Liver pathology was evident only in mice and was in the form of hypertrophy of centrilobular and mid-zonal hepatocytes (male and female mice at 1000 mg/kg bw/d, male mice at 100 mg/kg bw/d) and increased cytoplasmic eosinophilia (male and female mice at 1000 mg/kg bw/d, male mice at 100 mg/kg bw/d). Kidney changes in mice differed from those in rats. In the mouse, the changes involving lower kidney weight (male and female mice at 1000 mg/kg bw/d) and decreased renal tubular vacuolation and cytoplasmic fat (male mice at 1000 mg/kg bw/d) were unlikely to be of toxicological concern. In the rat, kidney changes were toxicologically significant and included hypertrophy of collecting ducts (male and female rats at 325 mg/kg bw/d), tubular vacuolation (male and female rats at 75 and 325 mg/kg bw/d) and mineralization (male and female rats at 325 mg/kg bw/d, male rats at 75 mg/kg bw/d). Thyroid effects, in the form of follicular hyperplasia and hypertrophy, were observed in male rats only and then only at the highest dose level tested. Based on effects on body weight and liver pathology, the LOAEL and NOAEL in the mouse are 100 and 10 mg/kg bw/d, respectively. In the rats, based on body-weight effects and kidney pathology, the LOAEL and NOAEL are 75 and 10 mg/kg bw/d, respectively.

Mutagenicity data assessing gene mutation in microbial and mammalian cell systems as well as in vitro and in vivo chromosome aberration did not demonstrate genotoxic effects for cloransulam-methyl. DNA damage and repair endpoints were not assessed.

A two-generation reproductive toxicity study in rats showed that cloransulam-methyl at dietary levels of up to 500 mg/kg bw/d had no effects on reproductive parameters. But this dietary level caused a slight increase in F_1 pup mortality during lactation days 0–4. The viability indices of the F_1 pups are still within the historical range. The toxic effect observed in the F_1 offspring was probably related to systemic toxicity exhibited by the parental animals: lower body weight and body-weight gains in P_1 males (pre-mating period) and females (pre-mating and gestation periods) at 500 mg/kg bw/d. In parental animals, organ and tissue pathology was evident in the kidneys and possibly the thyroid. Kidney changes included higher relative kidney weight (male rats at 100 and 500 mg/kg bw/d), hypertrophy of the collecting tubules and vacuolation consistent with fatty changes of proximal tubules (mid- and high-dose males and females). Diffuse hypertrophy of thyroid follicular epithelial cells was observed in high-dose males and females. Based on the kidney effect, the LOAEL and NOAEL for parental toxicity are 100 and 10 mg/kg bw/d, respectively. The LOAEL and NOAEL for offspring toxicity are 500 and 100 mg/kg bw/d, respectively. The NOAEL for reproductive toxicity is 500 mg/kg bw/d, the highest dose level tested. Since the offspring viability effect in the F_1 was within the historical control range, the effect was not considered to indicate a quantitative sensitivity of the young.

Teratogenicity of cloransulam-methyl was assessed in the rat and rabbit. In the rat, oral doses of up to 1000 mg/kg bw/d, administered during gestation days 6–15, did not elicit any maternal or developmental toxicity. Thus, the NOAEL for maternal and developmental toxicity is 1000 mg/kg bw/d. In the rabbit, cloransulam-methyl at an oral dose of 300 mg/kg bw/d, administered during gestation days 7–19, led to maternal toxicity, manifested as reduced food intake, lower body weight, lower fecal output and two dams aborted. Thus, the LOAEL and NOAEL for maternal toxicity are 300 and 100 mg/kg bw/d, respectively. There were no effects on developmental toxicity and the NOAEL for developmental toxicity is 300 mg/kg bw/d, the highest dose level tested.

The acute neurotoxicity potential of cloransulam-methyl was assessed in rats that were given single oral doses of up to 2000 mg/kg bw. After dosing, the rats were assessed for mortality, clinical toxic signs, body weight, motor activity and functional observational battery. There were no treatment-related effects on the parameters assessed. Thus, the NOAEL for acute neurotoxicity is 2000 mg/kg bw/d. In a subchronic, 90-day neurotoxicity study, rats were tested up to 1000 mg/kg bw/d. The NOAEL was determined to be 1000 mg/kg bw/d as there were no treatment-related effects at this limit dose.

At this time, there is no evidence in the animal data to suggest an alteration of endocrine function as a result of exposure to cloransulam-methyl.

Toxicology studies on cloransulam-methyl and FirstRate Herbicide Water Dispersible Granules are summarized in Appendix I, Table 1.

3.2 Determination of Acceptable Daily Intake

Short-term and long-term toxicity data on cloransulam-methyl did not demonstrate significant toxicity concerns on oncogenicity, genotoxicity, teratogenicity, reproductive toxicity or neurotoxicity. There were no indications of a quantitative or qualitative sensitivity of the young. The most sensitive species tested was the dog. Based on the NOAEL of 5 mg/kg bw/d established in the one-year dog dietary toxicity study and the standard 100-fold safety factor, the recommended acceptable daily intake (ADI) for dietary risk assessment is 0.05 mg/kg bw/d.

3.3 Acute Reference Dose

The toxicological data assessed indicated the lack of acute toxicity hazards for cloransulam-methyl. Therefore, there is no need to establish an acute reference dose (ARfD) for acute risk assessment.

3.4 Occupational and Bystander Risk Assessment

Refer to REG2001-08 for a detailed assessment of the occupational and bystander risk for cloransulam-methyl and FirstRate Herbicide Water Dispersible Granules.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition for risk assessment and enforcement in plant products is cloransulam-methyl plus the acid cloransulam, calculated as parent ester. The data gathering/enforcement analytical methodology, gas chromatography with mass spectrometry (GC-MSD) method, is valid for the quantitation of cloransulam-methyl equivalent residues in soybean matrices. The residues of cloransulam-methyl equivalents are stable in soybean grain, forage and hay when stored in a freezer at -20°C for up to six months (forage, hay) and 12 months (soybean seed). Soybean grain was processed into hulls, dust, meal, crude oil and refined oil. There was no concentration of cloransulam-methyl equivalent residues in any of the soybean fractions. Supervised residue trials conducted throughout the United States in Canadian representative zones using the end-use product FirstRate Herbicide Water Dispersible Granules in or on soybean grain are sufficient to support the proposed maximum residue limits.

The residue analysis in plant products is summarized in Appendix I, Table 2.

3.5.2 Dietary Risk Assessment

A chronic dietary risk assessment was conducted using the Dietary Exposure Evaluation Model (DEEM–FCID, Version 2.0), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

3.5.2.1 Chronic Dietary Exposure Results and Characterization

The chronic dietary exposure from the supported cloransulam-methyl food use for all population groups is less than 0.000013 mg/kg bw/d (0.0%) of the acceptable daily intake (ADI). Aggregate exposure from food and water is less than 0.000222 mg/kg bw/d, representing less than 0.4% of the ADI for all population groups (Appendix I, Table 3).

3.5.2.2 Acute Dietary Exposure Results and Characterization

No appropriate endpoint attributable to a single dose for the general population (including children and infants) was identified. Therefore, no dietary exposure assessment was conducted.

3.5.3 Aggregate Exposure and Risk

The aggregate risk for cloransulam-methyl consists of exposure from food and drinking water sources only. There are no residential uses.

3.5.4 Established Maximum Residue Limits

The nature of the residues in animal and plant matrices, analytical methodology, field trial data and chronic dietary risk estimates are summarized in Appendix I, Tables 3 and 4.

The established maximum residue limit on dry soybean is 0.01 ppm. For additional information on maximum residue limits (MRLs) in terms of the international situation and trade implications, refer to Appendix I, Table 5.

4.0 Impact on the Environment

Refer to REG2001-08 for a detailed assessment of the impact on the environment of cloransulam-methyl and FirstRate Herbicide Water Dispersible Granules.

The required description of the persistence and mobility of the major transformation products as presented in REG2001-08 has been submitted to the PMRA and has been found to be satisfactory.

Cloransulam-methyl is slightly persistent in soil and water. It is not expected to volatilize from water or moist soils. The principal routes of transformation are biotransformation in soil and phototransformation and biotransformation in aquatic environments. Laboratory data indicated a potential for the parent compound and major transformation products to leach in soil. The relatively short half-life in soil would partially mitigate the potential for leaching of the parent compound. Results from a field study also indicated that cloransulam-methyl and cloransulam acid did not leach. An analysis of the information provided demonstrated that transport of cloransulam-methyl and its major transformation products through the soil profile was negligible.

Cloransulam-methyl will pose a negligible risk to earthworms, honey bees, birds, wild mammals, fish, and crustaceans. Cloransulam-methyl, however, will pose a high risk to terrestrial plants, aquatic plants and algae.

4.1 Fate and Behaviour in the Environment

Terrestrial Environment
Cloransulam-methyl hydrolyzes very slowly at acidic and neutral pH. However, it hydrolyzes rapidly at pH 9 with a half-life of three days. Phototransformation on soil is not a principal route of transformation (half-life of 30 to 70 days). In laboratory studies with aerobic soil, the DT_{50} for XDE-565 ranged from 13 to 28 days. The major transformation products were XDE-565 acid, 5-OH-XDE-565 and 5-OH-XDE-565-acid.

The results from the adsorption study indicated that XDE-565 and the transformation product XDE-565-acid are not strongly absorbed in most soils. Under laboratory conditions, no volatile transformation products, other than CO_2, were detected from a clay loam soil and a silt loam soil.

Under field conditions in Wisconsin, cloransulam-methyl had a DT_{50} value of 6.6 days in sandy loam soil. The DT_{90} was 59.1 days. The maximum concentration of XDE-565-acid was 25% of applied parent compound and was <10% at 100 days postapplication. The residues of cloransulam-methyl and the transformation product, XDE-565-acid, were primarily detected in the 0–30 cm soil layer (5.7% of applied).

Fate and behaviour of cloransulam-methyl in the terrestrial environment are summarized in Appendix I, Table 6.

Aquatic Environment

Cloransulam-methyl hydrolyzes very slowly at acidic and neutral pHs. However, it hydrolyzes rapidly at pH 9 with a half-life of three days. Phototransformation on soil will not be an important route of transformation. However, photolysis in water is a principal route of transformation (half-life of 22 minutes). The major phototransformation products in water are XDE-565-sulfonic acid and XDE-565-sulfonamide. Under aerobic aquatic conditions, the half-life of XDE-565 is 25.6 days in the water phase. After 31 days, 76% to 82% of the radiolabel remained in the water column. The major transformation product was XDE-565-acid. Under anaerobic aquatic conditions, the half-life of the parent compound is approximately 16 days (total system). The major transformation products in water and sediment were XDE-565-acid and N-(2-carboxy-phenyl-6-chloro)-{1-methyl-5-(2-fluoroethenyl)-1,2,4-triazol-3-sulfonamide}. In the aqueous phase, 5-OH-XDE-565 acid was also detected as a major transformation product. Under anaerobic aquatic conditions at 5°C, the half-life of the parent compound was 237 days.

Fate and behaviour of cloransulam-methyl in the aquatic environment is summarized in Appendix I, Table 7.

4.2 Effects on Non-Target Species

A quotient method is used to estimate risk of potential adverse effects on non-target species. The risk quotient is calculated by dividing the exposure estimate by a value representing a toxicity endpoint. A screening level risk assessment is initially performed using the expected environmental concentrations (EECs) for a worst-case scenario (e.g. direct overspray of a body of water) and the most sensitive toxicity endpoint. Low risk is predicted if the risk quotient (RQ) is less than the trigger value of one. In these cases, no further assessment is done. For those groups of organisms for which the RQ is greater than one, a refined assessment is undertaken. A refined assessment takes into consideration more realistic exposure scenarios (e.g. drift to non-target habitats and runoff to water bodies) and may consider different toxicity endpoints.

4.2.1 Effects on Terrestrial Organisms (Appendix I, Tables 8 and 10)

The risk to non-target organisms was calculated using EEC values of 0.016 mg/kg in 15 cm depth of soil and 0.012 mg/L in 30 cm depth in water. The EEC in wildlife food sources, expressed in mg a.i./kg dw, will be 6.13, 1.18, 17.66, 17.55 and 23.19 for the bobwhite quail, mallard ducks, rats, mice and rabbits, respectively. Risk quotients were calculated using the NOEC, or an estimated NOEC equivalent to 1/10 of the EC_{50} or LC_{50}, or an estimated NOEC equivalent to 1/10 of the EC_{50} or LC_{50} for the most sensitive species per group.

Terrestrial Invertebrates

The major route of exposure for earthworms is through ingested soil in treated soybean fields. The risk quotient, based on a 14-day NOEC of 116 mg a.i./kg soil, was calculated as 1.38×10^{-4}; thus, earthworms are not expected to be at risk from the proposed use of FirstRate Herbicide

Water Dispersible Granules. The major route of exposure to honey bees is through contact with contaminated flowering plants. Cloransulam-methyl is classified as relatively non-toxic to honey bees on an acute contact basis. Using the assumptions of Atkins et. al. (1981), an $LD_{50} > 25$ µg a.i./bee would be equivalent to an application rate of >30 kg a.i./ha that would kill 50% of bees foraging in treated fields at the time of application or shortly afterwards. The risk quotient, therefore, is 1.25×10^{-3}. As the application rate is 0.035 kg a.i./ha, bees are not expected to be at risk from the use of FirstRate Herbicide Water Dispersible Granules.

Avian Species

The major risk to avian species is through ingestion of food sources contaminated by exposure to cloransulam-methyl during application. The risk quotients for dietary and reproductive effects, based on an eight-day dietary NOEC for bobwhite quail of 6520 mg a.i./kg diet and a reproductive NOEC for the mallard duck of 125 mg a.i./kg diet, are 1.09×10^{-3} and 9.44×10^{-3}, respectively. There is no risk from the acute oral route. Therefore, birds are not considered to be at risk from the use of FirstRate Herbicide Water Dispersible Granules.

Terrestrial Plants

The most sensitive species tested was the radish. Based on the EC_{25} value of 0.099 g a.i./ha for the radish, the risk quotient is 388.8. Therefore, the use of FirstRate Herbicide Water Dispersible Granules poses a risk to non-target terrestrial plants.

Small Wild Mammals

The major risk to small mammals is through ingestion of food sources contaminated by exposure to cloransulam-methyl during application. For acute oral toxicity in rats, the risk quotient is expressed as 5660 days of intake required to produce the equivalent of the dose administered to kill 50% of the laboratory population. The risk quotient for dietary toxicity in mice is 3.51×10^{-1} based on the NOAEL for the males, which was 50 mg/kg bw/d. Therefore, the use of FirstRate Herbicide Water Dispersible Granules does not pose a risk to small wild mammals.

Toxicity of cloransulam-methyl to non-target terrestrial organisms is summarized in Appendix I, Table 8 and the screening level risk assessment on non-target species risk to terrestrial organisms is summarized in Appendix I, Table 10.

4.2.2 Effects on Aquatic Organisms (Appendix I, Tables 9 and 11)

The major source of contamination of aquatic environments is through direct overspray. Based on a 48-h NOEC of 63.3 mg a.i./L for daphnids, a 96-h NOEC of 121 mg a.i./L for shrimp and a 96-h NOEC of 86 mg a.i./L for rainbow trout, the risk quotients for these species are 1.9×10^{-4}, 9.9×10^{-5} and 1.4×10^{-4}, respectively. Therefore, these species are not considered to be at risk from the use of FirstRate Herbicide Water Dispersible Granules.

Based on the 96-h NOEC for the green alga *(Selenastrum capricornutum)* of 0.9 µg a.i./L and a 14-d NOEC for duckweed of 0.78 µg a.i./L, the risk quotients for algae and duckweed are 13.3 and 15.3, respectively. Therefore, the use of FirstRate Herbicide Water Dispersible Granules poses a risk to non-target aquatic plants.

Toxicity of cloransulam-methyl to non-target aquatic organisms is summarized in Appendix I, Table 9, and the screening level risk assessment on non-target species risk to aquatic organisms is summarized in Appendix I, Table 11.

5.0 Value

Refer to REG2001-08 for a detailed assessment of the value and efficacy of FirstRate Herbicide Water Dispersible Granules.

6.0 Formulants and Microcontaminants of Health and Environmental Concern

6.1 Toxic Substances Management Policy Considerations

The management of toxic substances is guided by the federal government's Toxic Substances Management Policy, which puts forward a preventive and precautionary approach to deal with substances that enter the environment and could harm the environment or human health. The policy provides decision makers with direction and sets out a science-based management framework to ensure that federal programs are consistent with its objectives. One of the key management objectives is virtual elimination from the environment of toxic substances that result predominantly from human activity and that are persistent and bioaccumulative. These substances are referred to in the policy as Track 1 substances.

During the review process, cloransulam-methyl and FirstRate Herbicide Water Dispersible Granules were assessed in accordance with the PMRA Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*. Substances associated with the use of cloransulam-methyl were also considered, including major transformation products formed in the environment, microcontaminants in the technical product and formulants in the end-use product, FirstRate Herbicide Water Dispersible Granules. The PMRA has reached the following conclusions:

- Cloransulam-methyl does not meet the criteria for persistence. Its values for half-life in water (25.6 days), soil (14–22 days), and sediment (16 days, in a water/sediment system) are below the TSMP Track 1 cut-off criteria for water (≥182 days), soil (≥182 days) and sediment (≥365 days). Persistence in air, although not known, is not a concern as there is a low potential for volatilization.

- Cloransulam-methyl is not bioaccumulative. Studies have shown that the *n*-octanol–water partition coefficient (log K_{ow}) is 1.12 at pH 5, which is below the TSMP Track 1 cut-off criterion of ≥5.0, and a fish bioaccumulation study was not triggered. The mammalian toxicology and livestock and poultry metabolism studies support the conclusion that cloransulam-methyl does not bioaccumulate.

- Therefore, the use of cloransulam-methyl is not expected to result in the entry of Track 1 substances into the environment.

6.2 Formulants of Health Concern

- Cloransulam-methyl (technical grade) does not contain any contaminants of health or environmental concern identified in the *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641-2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern.*

- The end-use product FirstRate Herbicide Water Dispersible Granules does not contain any formulants of health or environmental concern identified in the *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641-2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern.*

7.0 Summary

7.1 Human Health and Safety

The toxicology data submitted for cloransulam-methyl is adequate to define the majority of toxic effects that may result from human exposure to cloransulam-methyl. In subchronic and chronic studies on laboratory animals, target organs included the liver and kidneys. There was no evidence of increased susceptibility of the young in teratology studies. Cloransulam-methyl is not considered to be a neurotoxicant.

The nature of the residue in soybean, goat and hen is adequately understood. The residue definition is cloransulam-methyl and the acid, cloransulam calculated as parent ester. The proposed use of cloransulam-methyl in or on soybean does not constitute an unacceptable chronic dietary risk (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend maximum residue limits to protect human health. The Pest Management Regulatory Agency previously established the following maximum residue limit:

Residues of cloransulam-methyl in and on dry soybean treated with cloransulam-methyl are covered under an MRL of 0.01 ppm.

7.2 Environmental Risk

Data on the environmental fate and behaviour of cloransulam-methyl indicated that the chemical is slightly persistent in soil and water, with a low potential for carryover into the next growing season. Neither cloransulam-methyl nor its major transformation products are expected to enter groundwater. Cloransulam-methyl is not expected to enter the atmosphere.

Based on a first approximation of EEC, there is a risk to terrestrial and aquatic non-target plants in the absence of mitigation. These risks can be mitigated by the establishment of terrestrial and aquatic buffer zones.

A buffer zone of 35 m is required to protect non-target plant species for ground application. This value is based on the phytotoxicity to radish. A buffer zone of seven metres around all open

bodies of water, e.g. rivers, lakes, streams and ponds, is required to protect non-target aquatic species. This value is based on the NOEC for duckweed, the most sensitive aquatic species.

7.3 Value

The value data submitted supported the use of FirstRate Herbicide Water Dispersible Granules when applied according to the label directions.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing full registration for Cloransulam-methyl Technical Herbicide and the end-use product FirstRate Herbicide Water Dispersible Granules to control specific broadleaf weeds in soybeans grown in Eastern Canada. An evaluation of current scientific data from the registrant and scientific reports has resulted in the determination that, under the proposed conditions of use, the end-use product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

µm	micrometre(s)
a.i.	active ingredient
ALS	acetolactate synthase enzyme
ADI	acceptable daily intake
ARfD	acute reference dose
bw	body weight
d	day(s)
cm	centimetre(s)
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in the test population)
DT_{90}	dissipation time 90% (the dose required to observe a 90% decline in the test population)
EC_{50}	effective concentration on 50% of the population
EEC	expected environmental concentration
F_1	first filial generation
FDA	*Food and Drugs Act*
FOB	functional observation battery
GC-MSD	gas chromatography with mass spectrometry detection
GSD	geometric standard deviation
ha	hectare(s)
Hb	hemoglobin
HCT	hematocrit
HDT	highest dose tested
kg	kilogram(s)
L	litre(s)
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOD	limit of detection
log K_{ow}	*n*-octanol–water partition coefficient
m	metre(s)
MAS	maximum average score
mg	milligram(s)
MIS	maximum irritation score
MMAD	mass median aerodynamic diameter
MRL	maximum residue limit
NOEC	no observed effect concentration
NOAEL	no observed adverse effect level
P_1	pre-mating period
PMRA	Pest Management Regulatory Agency
pH	-log 10 hydrogen ion concentration
ppm	parts per million
RAC	raw agricultural commodity
RBC	red blood cell

RQ	risk quotient
SGPT	serum glutamate pyruvate transaminase
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy

Appendix I

Table 1 Summary Table of Toxicology Studies on Cloransulam-methyl (technical grade active ingredient) and FirstRate Herbicide Water Dispersible Granules (end-use product)

Study	TGAI, Purity, Species, Strain and Doses	NOAEL or LOAEL (mg/kg bw/d)	Target Organ and Significant Effects and Comments
METABOLISM			
In a metabolism study, ^{14}C-XDE-565, uniformly ^{14}C-labelled in the aniline ring (purity of unlabelled XDE-565 = 97.3%) was administered to 5 Fischer 344 rats/sex/dose by gavage either as a single dose of 5 or 1000 mg ^{14}C-XDE-565/kg bw or as 14 daily oral doses of 5 mg/kg bw/d of non-radiolabelled XDE-565 followed by a single 5 mg/kg bw oral dose of ^{14}C-XDE-565 on day 15. Excretion of radioactivity (^{14}C) was followed for 72 h postdosing. The rats were then terminated and radioactivity in tissues and carcass were measured. Urine and fecal samples were analyzed by HPLC and DIP–MS. Overall, 91–102% of the administered radioactivity in each dose regiment was recovered. The overwhelming percentage of the radioactivity was recovered in urine and feces. However, there were both sex and dose differences. At the low dose of 5 mg/kg bw, males excreted nearly equivalent amounts of radioactivity in urine and feces (41–52%) while females excreted approximately 3.5 times more radioactivity in urine than in feces (68–80% versus 21%). At the high dose of 1000 mg/kg bw, fecal excretion of radioactivity predominated, 83% of the administered radioactivity was eliminated in the feces of males and 78% in females. Urinary elimination was 10% and 17% in males and females, respectively. Half-lives calculated from the elimination of the 5 mg/kg bw doses were 6.5 h for females and 8–8.5 h for males, while the half-lives following the 1000 mg/kg bw dose were 7.9 h for females and 13.2 h for males. Only a small fraction (≤2.3%) of the administered radioactivity remained in the tissues and carcass 72 h postdosing. Blood, kidneys and liver contained the highest concentrations of radioactivity (i.e. 0.04–0.03% dose/g). The remaining tissues contained ≤0.018% dose/g. Analysis of metabolite profile using HPLC indicated up to 10 peaks found in urine and 3 in feces. Females eliminated a greater percentage of the 5 mg/kg bw dose in urine as unchanged XDE-565 than males (~50% versus 22%). Males eliminated a greater percentage of the 5 mg/kg bw dose in the feces as metabolites (~28% versus 10%). Both sexes eliminated 15–22% of the 5 mg/kg bw dose in the urine as metabolites. Less than 8% of the 5 mg/kg bw dose was excreted in the feces unchanged but over 70% of the 1000 mg/kg bw dose was excreted as unchanged XDE-565 in the feces. The only metabolite identified had a hydroxyl group in the aromatic ring of XDE-565. Incomplete absorption of the 1000 mg/kg dose is used to account for the dose-dependent differences observed in the disposition of XDE-565. Sex-dependent differences in disposition of the 5 mg/kg bw dose were traced to more efficient elimination of unchanged XDE-565 by the female kidneys.			

Study	TGAI, Purity, Species, Strain and Doses	NOAEL or LOAEL (mg/kg bw/d)	Target Organ and Significant Effects and Comments
In a second metabolism study, ^{14}C-XDE-565 (99% purity), uniformly labelled at the 7 and 9 positions on the triazolo-pyrimidine ring, was administered to 3 Fischer 344 rats/sex by gavage as a single dose of 5 mg/kg bw/d. Approximately 94% of the administered dose was recovered in urine, feces, cage wash, tissues and carcass. Clear sex-related differences in the routes of elimination were observed. Male rats excreted about equal amounts of radioactivity in the urine (37–39%) and feces (48–51%). In females, the principal excretion route was the urine (70–72%) while the feces (20–22%) was the minor excretion route. The tissues and carcass accounted for less than 5% of the administered dose at 72 h postdosing for both sexes. Characterization of metabolites by HPLC indicated up to 11 separate radiolabelled peaks in the urine and up to 8 peaks in fecal samples. The identified urinary metabolites were the unchanged parent compound, 4-OH-phenyl-XDE-565, OH-pyrimidine-XDE-565 and XDE-565-7-*N*-acetylcysteine. The identified fecal metabolites were the unchanged parent compound and 4-OH-phenyl-XDE-565. The metabolism data indicated that the excretion and metabolism of ^{14}C-XDE-565 labelled on the triazolo-pyrimidine ring were similar to the excretion and metabolism of ^{14}C-XDE-565 labelled on the aniline ring.			
ACUTE STUDIES: Technical grade active ingredient			
Oral	**Cloransulam-methyl** 97.3%, AGR 293032; rat, Fischer 344, 5/sex; 5000 mg/kg bw in 50% solution (9:1 corn oil: acetone) by gavage	LD_{50}: ♂ + ♀ > 5000 mg/kg bw	No mortality, clinical signs, gross pathology; all rats gained weight. **Low toxicity**
Dermal	**Cloransulam-methyl** 97.3%, AGR 293032; rabbit, NZW, 5/sex; 2000 mg/kg bw	LD_{50}: ♂ + ♀ > 2000 mg/kg bw	No mortality, clinical signs, gross pathology; all animals gained weight; skin reaction was apparently not assessed. **Low toxicity**
Inhalation (4-h nose-only)	**Cloransulam-methyl** 97.3%, AGR 293032; rat, Fischer 344, 5/sex; 3.77 mg/L (actual), 9.64 mg/L (nominal), MMAD ± GSD = 1.86 µm ± 2.63	LC_{50}: ♂ + ♀ > 3.77 mg/L (actual)	No mortality, clinical signs, gross pathology; all animals lost weight initially but gained weight by day 8. **Low toxicity**
Eye irritation	**Cloransulam-methyl** 97.3%, AGR 293032; rabbit, NZW, 1 ♂ + 5 ♀; 0.1 g/eye	Maximum average score (MAS) at 1 h = 3/110	Maximum average irritation scores at 1, 24, 48 and 72 h = 3.0, 0.67, 0, 0 of 110, respectively. **Minimally irritating**
Skin irritation	**Cloransulam-methyl** 97.3%, AGR 293032; rabbit, NZW; 0.5 g/rabbit	Maximum irritation score (MIS) = 0/8	No skin reactions at 0.5, 24, 48 and 72 h postdosing. **Non-irritating**

Study	TGAI, Purity, Species, Strain and Doses	NOAEL or LOAEL (mg/kg bw/d)	Target Organ and Significant Effects and Comments
Skin sensitization (Buehler method)	**Cloransulam-methyl** 97.3%, AGR 293032; guinea pig, Hartley albino induction: 0.4 g, 100% challenge: 0.4 g, 100%		Study was rejected because the test article was not moistened with a vehicle such as water. Based on the dermal sensitization data on FirstRate®, cloransulam-methyl is not expected to be a dermal sensitizer.
ACUTE STUDIES: END-USE PRODUCT (NAF-75)			
Oral	**NAF-75** A946-23; rat, Fischer 344, 5/sex; 5000 mg/kg bw in distilled water	LD_{50}: ♂ + ♀ > 5000 mg/kg bw	No mortality or gross pathology; all rats gained weight; clinical findings included urine and fecal soiling in perineal area, loose stool and salivation. **Low toxicity**
Dermal	**NAF-75** A946-23; rabbit, NZW, 5/sex; 2000 mg/kg bw moistened with distilled water	LD_{50}: ♂ + ♀ > 2000 mg/kg bw	No mortality, clinical signs, gross pathology; all animals gained weight; erythema noted at all test skin sites. **Low toxicity**
Inhalation			No data; based on high % of technical active in end-use product, low acute inhalation toxicity of technical active and no evidence of active toxicity of non-active ingredients. NAF-75 is estimated to be of **low toxicity.**
Eye irritation	**NAF-75** A946-23; rabbit, NZW; 3/sex; 0.1 g/eye	MIS = 7/110 at 1 h	**Minimally irritating**
Skin irritation	**NAF-75** A946-23; rabbit, NZW, 4♂ + 2♀; 0.5 g/rabbit, moistened with water	MIS = 1.5/8 at 0.5 h	**Slightly irritating**
Skin sensitization (Buehler method)	**NAF-75** A946-23; guinea pig, Hartley albino induction: 0.4 mL, 100% challenge: 0.4 mL, 30% vehicle = distilled water		Negative **Not a dermal sensitizer**

Study	TGAI, Purity, Species, Strain and Doses	NOAEL or LOAEL (mg/kg bw/d)	Target Organ and Significant Effects and Comments
SHORT-TERM TOXICITY: END-USE PRODUCT (NAF-75)			
21-d dermal rabbit	**NAF-75** A946-23; rabbit, NZW, 5/sex/group; 0, 100, 500, 1000 mg/kg bw/d	NOAEL: ♂ = 1000 ♀ = 500 LOAEL: ♂ > 1000 ♀ = 1000 mg/kg bw/d	No effects on mortality, clinical signs, food intake, bw, clinical chemistry, organ weight, gross pathology and histopathology 1000 mg/kg bw/d: ♀ anemic, ↓ RBC and HCT, ↑ white blood cell count
SHORT-TERM TOXICITY: Technical active			
90-d dietary mouse	**Cloransulam-methyl** 97.3%, AGR 0293032; mouse, B6C3F$_1$, 10/sex; dietary at 0, 50, 100, 500, 1000 mg/kg bw/d	NOAEL: ♂ = 50 ♀ = 100 LOEL: ♂ = 100 ♀ = 500 mg/kg bw/d	No effects on mortality, clinical signs of toxicity, ophthalmoscopy, bw, bw gain, food intake, gross pathology. >100: ♂ liver pathology (histologic changes) >500: ♀ liver pathology (histologic changes) ♂ + ♀: ↑ alkaline phosphatase activity Terminal bw of control mice: ♂ = 30.9 ± 2.5, ♀ = 25.5 ± 1.4 g (n = 10/sex) Terminal food intake of control mice: ♂ = 5.4 ± 1.2 (n = 10), ♀ = 7.3 ± 1.4 g/mouse/d (n = 6)
90-d dietary rat with 4-wk recovery	**Cloransulam-methyl** 97.3%, AGR 0293032; rat, Fischer, 5/sex/group; 0, 100, 500, 1000 mg/kg bw	NOAEL not determined LOAEL = 100 mg/kg bw/d	<u>Treatment</u> No effects on clinical signs, mortality, hematology, clinical chemistry or organ weight. >100: ♀ increased incidence of fatty vacuolation in the proximal tubules; ♂ hypertrophy of the collecting duct cells in males >500: ♂ + ♀ ↓ in body weight, body-weight gain, food consumption and specific gravity of urine; ♂ increased incidence of fatty vacuolation in the proximal tubules; ♀ hypertrophy of the collecting duct cells in males <u>Recovery</u> ♂ + ♀: all adverse effects showed reversibility at all doses

Study	TGAI, Purity, Species, Strain and Doses	NOAEL or LOAEL (mg/kg bw/d)	Target Organ and Significant Effects and Comments
2-wk palatability and toxicity dog	**Cloransulam-methyl** 99%, ACPR-353-12; dog, beagle, 1/sex/group; dietary at 0, 50, 100, 200, 500, 1000 mg/kg bw/d	No effects at ≤200 mg/kg bw/d	1000: ↓ bw, food intake, platelet counts >500: gross pathology (multiple hemorrhages in various organs and tissues) Liver pathology: infiltration of inflammatory cells and degenerative hepatocytes ≤200: no effects
90-d dietary dog	**Cloransum-methyl** 97.3%, DECO-60-77; dog, beagle, 4/sex/group; dietary at 0, 40, 200 and 400 mg/kg bw/d	NOAEL = 40 mg/kg bw/d LOAEL = 200 mg/kg bw/d	>200: ♂ + ♀ ↓ red blood cell parameters, ↑ absolute and relative thyroid weights accompanied by hypertrophy and ↓ colloid, decrease in body weight and body-weight gain, ♂ ↓ absolute and relative testes weights with ↓ spermatogenesis and degeneration of the epithelium of the seminiferous tubules ♀ death at 200 mg/kg bw/d dose 400: head bobbing, stiffness of gait and slowed movements
1-yr dietary dog	**Cloransulam-methyl** 98.2%, TSN100049; dog, beagle, 4/sex/group; 0, 5, 10, 50 mg/kg bw/d	NOAEL = 5 mg/kg bw/d LOEL = 10 mg/kg bw/d	No effects on mortality, clinical signs, food intake, bw, bw gain, ophthalmoscopy, hematology, urinalysis, organ weight, gross pathology 50: ♂ + ♀ ↓ albumin, ↑ AP, SGPT, liver histopathology 10: ♂ + ♀ ↑ AP, SGPT, liver histopathology
21-d dermal rabbit	**Cloransulam-methyl** 98.2%, TSN100049; rabbit, NZW, 5/sex/group; 0, 100, 500, 1000 mg/kg bw/d	NOAEL: ♂ = 1000 ♀ = 500 LOEL: ♂ > 1000 ♀ = 1000 mg/kg bw/d	No effects on mortality, clinical signs, dermal findings, food intake, bw, clinical chemistry, organ weight, gross pathology and histopathology 1000: ♀ anemic, ↓ RBC, Hb, HCT RBC: anisocytosis and macrocytosis

Study	TGAI, Purity, Species, Strain and Doses	NOAEL or LOAEL (mg/kg bw/d)	Target Organ and Significant Effects and Comments
LONG-TERM CHRONIC TOXICITY AND ONCOGENICITY			
2-yr dietary oncogenicity mouse	**Cloransulam-methyl** 98.2%, DECO-343-6; mouse, B6C3F11, 60/sex/group (10/sex/group sacrificed at 12 months); 0, 10, 100, 1000 mg/kg bw/d	NOAEL = 10 mg/kg bw/d LOEL = 100 mg/kg bw/d No evidence of oncogenic potential	Mortality (wk 104, based on 50/sex/group): ♂ = 5, 7, 8, 9; ♀ = 12, 8, 14, 8 at 0, 10, 100 and 1000 mg/kg bw/d, respectively) No effects on mortality, clinical signs, food intake, feed efficiency, ophthalmoscopy or hematology 1000: ♂ + ♀ ↓ bw gain 100: ♀ ↓ bw gain 10: no effects
2-yr dietary chronic and oncogenicity rat	**Cloransulam-methyl,** 98.2%, DECO-343-6; rat, Fischer 344, 60/sex/group (10/sex/group for interim sacrifice at 52 weeks); 0, 10, 75, 325 mg/kg bw/d	NOAEL = 10 mg/kg bw/d LOEL = 75 mg/kg bw/d No evidence of oncogenic potential	Mortality (wk 104, based on 50/sex/group): ♂ = 20, 27, 16, 8; ♀ = 7, 12, 8, 13 at 0, 10, 75 and 325 mg/kg bw/d, respectively) No effects on mortality, food intake, feed efficiency, ophthalmoscopy, hematology, clinical chemistry, organ weights, gross pathology 325: ♂ + ♀ perineal soiling at 12 and 24 months, ↓ bw and bw gain, kidney histopathology 75: ♂ + ♀ perineal soiling at 12 and 24 months, kidney histopathology 10: ♂ + ♀ perineal soiling at 24 months
MUTAGENICITY			
Study	**Species, Strain or Cell Type**	**Doses Employed**	**Significant Effects and Comments**
In vitro *Salmonella* and Ames test	**Cloransulam-methyl** 97.3%, AGR 0293032; *S. typhimurium*: TA98, TA100, TA1535, TA1537	-S9: 0, 0.05, 0.15, 0.5, 1.5, 5 µg/plate +S9: 0, 0.15, 0.5, 1.5, 5, 15 µg/plate	Negative
In vitro CHO HGPRT gene mutation	**Cloransulam-methyl** 98.2%, TSN100049 CHO-K1-BH_4	±S9: 50, 100, 200, 400, 600, 800 µg/mL	Negative

Study	TGAI, Purity, Species, Strain and Doses	NOAEL or LOAEL (mg/kg bw/d)	Target Organ and Significant Effects and Comments
In vitro chromosome aberration in rat lymphocytes	**Cloransulam-methyl** 97.3%, AGR 0293032; rat, SD; primary rat peripheral blood lymphocytes; 2 independent assays	±S9: 4-h exposure Assay 1: 0, 6, 20, 60, 200, 600 µg/mL Assay 2: 0, 53, 183, 6000 µg/mL Positive controls: –S9: Mitomycin C +S9: cyclophosphamide cells harvested at 24 and 48 h	Negative
Micronucleus assay (in vivo)	**Cloransulam-methyl** 97.3%, AGR 0293032; mouse CD-1, ♂ + ♀, 5/sex/group; bone marrow	0, 500, 1667, 5000 mg/kg bw; 1000 polychromatic RBC/mouse assessed at 24, 48, 72 h	Negative
REPRODUCTION AND DEVELOPMENTAL TOXICITY			
2-generation dietary reproductive toxicity (rat), 1 litter per generation	**Cloransulam-methyl** 98.2%, TSN100049; rat, SD, 30/sex/group; at 0, 10, 100, 500 mg/kg bw/d (ppm equivalent: mean of all time intervals: ♂ = 0, 165, 1695, 8813 ♀ = 0, 123, 1410, 6263)	Parental systemic toxicity: LOEL = 100 mg/kg bw/d NOAEL = 10 mg/kg bw/d Reproductive toxicity: NOAEL = 500 mg/kg bw/d, HDT Offspring toxicity: LOEL = 500 mg/kg bw/d NOAEL = 100 mg/kg bw/d	Reproductive performance: no treatment-related effects Parental effects: 500: P_1 ♂ + ♀: ↓ bw and bw gain (pre-mating and gestation periods) ≥100: ♂ kidney pathology (↑ weight, histopathology) ♀ kidney pathology (histopathology) Offspring toxicity: 500: ↑ F_1 pup death during lactation d 0–4, viability indices within historical range
Teratology probe (rat)	**Cloransulam-methyl** 97.4%, AGR 293032; rat, SD, 10 mated ♀/group; 0, 100, 500, 1000 mg/kg bw/d in 0.5% aqueous Methocel A4M by gavage from gestation d 6–15; sacrificed on gestation d 16	No treatment-related effects	No treatment-related effects on maternal toxicity; embryotoxicity was not assessed.

Study	TGAI, Purity, Species, Strain and Doses	NOAEL or LOAEL (mg/kg bw/d)	Target Organ and Significant Effects and Comments
Teratology (rat)	**Cloransulam-methyl** 97.4%, AGR 293032; rat, SD, 30 mated ♀/group; 0, 100, 500, 1000 mg/kg bw/d in 0.5% aqueous Methocel A4M by gavage from gestation d 6–15; sacrificed on gestation d 21	LOAEL for maternal and developmental toxicity > 1000 mg/kg bw/d NOAEL for maternal and developmental toxicity = 1000 mg/kg bw/d No evidence of teratogenicity	Number of litters assessed: 28, 29, 27, 29, respectively for 0, 100, 500, 1000 mg/kg bw/d Maternal toxicity: none Fetotoxicity: none
Teratology probe (rabbit)	**Cloransulam-methyl** 98.2%, TSN100049; rabbit, NZW; 7 inseminated ♀/group at 0, 100, 500, 1000 mg/kg bw/d in 0.5% aqueous Methocel A4M by oral gavage on gestation d 7–19; sacrificed on gestation d 20	No effects at 100 mg/kg bw/d	Maternal toxicity: ≥500: ↓ food intake, bw, bw gain, fecal output 100: no treatment-related effects Embryotoxicity was not assessed.
Teratology (rabbit)	**Cloransulam-methyl** 98.2%, TSN100049; rabbit, NZW; 20 inseminated ♀/group at 0, 30, 100, 300 mg/kg bw/d in 0.5% aqueous Methocel A4M by oral gavage on gestation d 7–19; sacrificed on gestation d 28	LOAEL (mg/kg bw/d): Maternal toxicity = 300 Developmental toxicity > 300 NOAEL (mg/kg bw/d): Maternal toxicity = 100 Developmental toxicity = 300 Not teratogenic	Litters assessed: 18, 17, 16, 14 respectively for 0, 30, 100, 300 mg/kg bw/d Maternal toxicity: 300: ↓ bw, food intake, fecal output; 2 dams aborted due to anorexia Developmental toxicity: no treatment-related effects
SPECIAL STUDIES			
Acute neurotoxicity	**Cloransulam-methyl** 97.3%, TSN100049; rat, Fischer; 10/sex/group; 0, 200, 1000, 2000 mg/kg bw in 0.5% aqueous methylcelluose	NOAEL for acute neurotoxicity > 2000 mg/kg bw	No deaths, clinical signs, bw, bw gain, motor activity, FOB assessment, no histopathological findings in nervous tissues (5/sex of control and high-dose groups examined)
90-d neurotoxicity	**Cloransulam-methyl** 97.3%, AGR 0293032 rat, Fischer; 5/sex/group 0, 100, 500, 1000 mg/kg bw/d	NOAEL for subchronic neurotoxicity >1000 mg/kg bw	No deaths, clinical signs, bw, bw gain, motor activity, FOB assessment, no histopathological findings in nervous tissues (5/sex of control and high-dose group examined)

Study	TGAI, Purity, Species, Strain and Doses	NOAEL or LOAEL (mg/kg bw/d)	Target Organ and Significant Effects and Comments
Compound-induced mortality: Not evident as demonstrated below: • acute oral toxicity in rats at 5000 mg/kg bw • acute dermal toxicity in rabbits at 2000 mg/kg bw • acute inhalation toxicity in rats at 3.77 mg/L (actual, 4-h nose only exposure) • short-term (90-d) dietary toxicity in mice at up to 1000 mg/kg bw/d • short-term (2-wk) dietary toxicity in dogs at up to 1000 mg/kg bw/d • short-term (1-yr) dietary toxicity in dogs at up to 50 mg/kg bw/d • short-term (21-d) dermal toxicity in rabbits at up to 1000 mg/kg bw/d • long-term (2-yr) dietary toxicity in mice at up to 1000 mg/kg bw/d • long-term (2-yr) dietary toxicity in rats at up to 325 mg/kg bw/d			
Recommended ARfD: None; no acute toxicity hazards are expected.			
Recommended ADI: 0.05 mg/kg bw/d, based on the NOAEL of 5 mg/kg bw/d established in the 1-yr dog study and the standard safety factor of 100			
Recommended NOAEL for occupational risk assessment: 500 mg/kg bw/d established in the 21-d dermal toxicity studies of cloransulam-methyl and FirstRate® Herbicide (end-use product) in rabbits			

Table 2 Residue Analysis in Plant Products

Matrix	Method ID	Analyte	Method Type	LOQ	Reference
Plant	GRM 94.07	Cloransulam-methyl as parent ester	GC-MSD	0.01 ppm soybean grain, forage, hay	1187724 1187725 1187690
	GRM 94.09	Cloransulam-methyl as parent ester	GC-MSD	0.01 ppm soybean meal, hulls, crude oil, refined oil	1187701

Table 3 Integrated Food Residue Chemistry Summary

Nature of the Residue in Soybean—Postemergent Treatment		
Radiolabel	Aniline-UL-^{14}C	Triazolopyrimidine-7,9-^{14}C
Test site	In the field, a small subset of treated soybeans was covered with polystyrene boxes kept in the dark; another subset was exposed to sunlight.	
Treatment	Postemergent treatment; 43 days after planting at growth stage V5.	
Rate	88.8 g a.i./ha	87.9 g a.i./ha
End-use product	84% a.i. water dispersible granules	
Preharvest interval	0 (forage), 1 (forage-light), 1 (forage-dark), 20 (forage), 98 days (soybeans)	

The degradation pathway in plants following a postemergent application was postulated to proceed through homoglutathione adduct formations and photolysis. The triazolopyrimidine sulfonic acid and related metabolites were formed as a result of photolysis of cloransulam-methyl to cleave the bridging bond. The total radioactive residues (TRR) were different between the aniline-^{14}C and triazolopyrimidine-^{14}C labels for forage and soybeans. The TRRs in the early forage samples were from 4.4 to 9.4 ppm for the aniline-label study, and 9.4 to 10.8 ppm for the triazolopyrimidine-label study. Residues in the late forage (20 days after application) were 0.71 ppm and 1.05 ppm for the aniline and the triazolopyrimidine-label studies, respectively. Mature harvest soybeans had levels of 0.019 ppm (aniline-label) and 0.007 ppm (triazolopyrimidine-label).

Metabolites Identified	**Major Metabolites (>10% TRR)**		**Minor Metabolites (<10% TRR)**	
Radiolabel	**Aniline-UL-^{14}C**	**Triazolopyrimidine-7,9-^{14}C**	**Aniline-UL-^{14}C**	**Triazolopyrimidine-7,9-^{14}C**
Forage (0 day)	Cloransulam-methyl	Cloransulam-methyl	Cloransulam-methyl Cloransulam-methyl-cysteine Cloransulam-methyl-homoglutathione	Cloransulam-methyl-cysteine Triazolopyrimidine sulfonic acid Cloransulam-methyl-homoglutathione
Forage - light (1 day)	Cloransulam-methyl Cloransulam-methyl-cysteine	Cloransulam-methyl Cloransulam-methyl-cysteine	Cloransulam-methyl-homoglutathione 5-hydroxy-cloransulam-methyl	Triazolopyrimidine sulfonic acid Triazolopyrimidine-cysteine Cloransulam-methyl-homoglutathione 5-hydroxy-cloransulam-methyl
Forage - dark (1 day)	Cloransulam-methyl Cloransulam-methyl-cysteine	Cloransulam-methyl	Cloransulam-methyl-homoglutathione 5-hydroxy-cloransulam-methyl	Cloransulam-methyl-cysteine Triazolopyrimidine sulfonic acid Triazolopyrimidine-cysteine Cloransulam-methyl-homoglutathione

Forage (20 days)	—	—	Cloransulam-methyl Cloransulam-methyl-cysteine Cloransulam-methyl-triazoloacetic acid lignin, cellulose	Cloransulam-methyl-cysteine Triazolopyrimidine sulfonic acid Triazolopyrimidine-cysteine Cloransulam-methyl cloransulam-methyl-triazoloacetic acid lignin, cellulose
Soybeans	Protein, whey, polysaccharides	Protein, whey, polysaccharides	—	—
The residue definition is cloransulam-methyl and the acid clorasulam, calculated as parent ester. The proposed analytical method converts acid residues to the parent ester by derivitization with a methylating agent.				

Confined Rotational Crop Study—Lettuce, Potatoes, Wheat	
Radiolabel	Aniline-UL-^{14}C and Triazolopyrimidine-7,9-^{14}C
Test Site	Microplots in screenhouses
Treatment	Application to bare soil; incorporated lightly 1 day following application.
Rate	55 g a.i./ha
End-use product	Cloransulam-methyl dissolved in acetone
Plantback interval	120 days

Cloransulam-methyl is extensively metabolized with the majority of the radioactivity found in naturally occurring compounds (starch in the grain and lignin, cellulose, and higher molecular weight of polysaccharides, oligosaccharides and proteins in straw).

Metabolites Identified	**Major Metabolites (>10% TRR)**		**Minor Metabolites (<10% TRR)**	
Radiolabel	**Aniline-UL-^{14}C**	**Triazolopyrimidine-7,9-^{14}C**	**Aniline-UL-^{14}C**	**Triazolopyrimidine-7,9-^{14}C**
Lettuce	—	—	—	—
Potato	—	—	—	—
Wheat forage	—	—	—	—
Wheat grain	Starch	Starch	Cloransulam-methyl	Cloransulam-methyl
Wheat straw	Cellulose	Cellulose	Cloransulam-methyl, lignin	Cloransulam-methyl, lignin, Triazolopyrimidine sulfonic acid

The confined crop rotation study supports the residue definition as outlined in the plant metabolism studies. The study supports the proposed plantback intervals.

Nature of the Residue in Lactating Goat			
Species	**Radiolabel**	**Dose Level**	**Sacrifice**
Carpa	Aniline-UL-^{14}C	10.56 ppm in feed	24 hours after the final dose.
	Triazolopyrimidine-7,9-^{14}C	10.17 ppm in feed	
Radiolabelled cloransulam-methyl was administered to goats once daily for five consecutive days. The majority of the radioactivity was excreted in urine and feces (74% to 86% of the TRR). The GI tract and contents contained an average of 6% of the administered dose. The %TRR in the tissues, milk and blood samples were less than 0.1% of the administered dose. The highest concentration of residues in tissues were found in kidneys, with an average of 0.125 ppm for both radiolabels, followed by liver (0.046 ppm), blood (0.036 ppm), muscle (0.002 ppm), milk and fat (< 0.001 ppm).			

Metabolites Identified	**Major Metabolites (>10% TRR)**		**Minor Metabolites (<10% TRR)**	
Radiolabel	**Aniline-UL-^{14}C**	**Triazolopyrimidine-7,9-^{14}C**	**Aniline-UL-^{14}C**	**Triazolopyrimidine-7,9-^{14}C**
Liver	Cloransulam	Cloransulam	Cloransulam-methyl, 5-OH-cloransulam-methyl	Cloransulam-methyl, 5-OH-cloransulam-methyl
Kidney	Cloransulam-methyl	Cloransulam-methyl	Cloransulam	Cloransulam
The residue definition is cloransulam-methyl and the acid cloransulam, calculated as parent ester.				

Nature of the Residue in Laying Hen			
Species	**Radiolabel**	**Dose Level**	**Sacrifice**
Gallus domesticus	Aniline-UL-^{14}C	9.09 ppm in feed	24 hours after the final dose.
	Triazolopyrimidine-7,9-^{14}C	8.43 ppm in feed	
Radiolabelled cloransulam-methyl was administered to laying hens by capsules twice daily for five consecutive days. The majority of the residues were found in the excreta (85.0% to 87.8% of the TRR). Residue levels were less than 0.1% of the administered dose in tissues and eggs. The highest concentration of residues was in the liver (0.144 to 0.163 ppm), followed by eggs (0.015 to 0.018 ppm), muscle (0.005 to 0.036 ppm), and fat (0.003 to 0.006 ppm) for both radiolabels.			

Metabolites Identified	**Major Metabolites (>10% TRR)**		**Minor Metabolites (<10% TRR)**	
Radiolabel	**Aniline-UL-^{14}C**	**Triazolopyrimidine-7,9-^{14}C**	**Aniline-UL-^{14}C**	**Triazolopyrimidine-7,9-^{14}C**
Egg	Cloransulam-methyl	Cloransulam-methyl	—	—
Muscle	—	Cloransulam-methyl-sulfonamide	—	—
Liver	—	Cloransulam-methyl-sulfonamide	—	Cloransulam-methyl-sulfonamide
The residue definition is cloransulam-methyl and the acid cloransulam, calculated as parent ester.				

Crop Field Trials —Soybean

All of the trials were conducted in the United States between 1995 and 1997 in various crop regions (1, 2, 3, 4, 5 and 6). The pre-emergent trials were conducted with NAF-95, a water dispersible granule formulation containing 84.4% cloransulam-methyl. The postemergent trials included the non-ionic surfactant (Ortho X-77) and the liquid fertilizer (urea ammonium nitrate). The proposed pre-emergent rate is 35 g a.i./ha/season, and the early postemergent rate is 17.5 g a.i./ha/season with a PHI of 65 days.

Commodity	Total Rate g a.i./ha	PHI (days)	Cloransulam-methyl equivalent residues (ppm)			
			n	Min.	Max.	Median
Pre-emergent						
Grain	36.5–46.5	102–149	21	<0.003	<0.003	<0.003
Postemergent						
Grain	17.3–17.8	76–224	29	<0.003	<0.004	<0.003
Grain	44–87.5	92–145	3	<0.003	<0.003	<0.003
Forage	17.2–17.9	14–47	15	<0.003	0.321	<0.003
Hay	17.2–17.9	14–47	15	0.0105	0.121	<0.005

Processing Studies —Soybean

In the processed food/feed study, cloransulam-methyl formulated as NAF-75 (84.4% a.i.), a water dispersible granule (WDG), was applied to soybeans as a postemergent spray in the 6–7 leaf stage at 87.5 g a.i./ha, which is fivefold the proposed postemergent application rate. The soybean grain harvested 76 days after application was processed into hulls, dust, meal, crude oil and refined oil.

Fraction	Cloransulam-methyl Residue Levels (ppm)	Calculated Processing Factor
Grain RAC	<0.005 (LOD)	—
Dust < 2540 µm	<0.005 (LOD)	—
Dust > 2540 µm	<0.005 (LOD)	—
Meal	<0.005 (LOD)	—
Hulls	<0.005 (LOD)	—
Crude oil	<0.005 (LOD)	—
Refined oil	<0.005 (LOD)	—

Storage Stability —Plant Matrices

Samples of soybean grain were spiked with cloransulam-methyl at a level of 0.20 ppm and were stored for a duration of 375 days. Samples of soybean forage and hay were stored for 188 days and 174 days, respectively.

Matrix	Demonstrated Storage		Actual Maximum Storage	
	Duration (days)	Temperature	Duration (days)	Temperature
Soybean grain	375	-20°C	86–370	-20°C
Soybean forage	188	-20°C	95–177	-20°C
Soybean hay	174	-20°C	95–174	-20°C

Livestock Feeding
The current label indicates not to graze the treated crops or cut for hay. However, since the feeding levels in the hen and goat metabolism studies were highly exaggerated (3600-fold (hen) and 190-fold (goat)), it is unlikely that hens or cattle fed treated crop would have residue levels detectable in any tissue, eggs or milk above 0.01 ppm.

Table 4 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES			
RESIDUE DEFINITION FOR ENFORCEMENT AND RISK ASSESSMENT **Primary crops (soybean)** **Rotational crops (lettuce, potatoes, wheat)**		Cloransulam-methyl, [3-Chloro-2-(((5-ethoxy-7-fluoro(1,2,4)triazolo(1,5-c)-pyrimidin-2-yl)sulfonyl)amino)benzoic acid methyl ester], plus the acid cloransulam, calculated as parent ester	
METABOLIC PROFILE IN DIVERSE CROPS		Only soybean was investigated	
ANIMAL STUDIES		**Ruminant**	
RESIDUE DEFINITION FOR ENFORCEMENT AND RISK ASSESSMENT		Cloransulam-methyl , [3-Chloro-2-(((5-ethoxy-7-fluoro(1,2,4)triazolo(1,5-c)-pyrimidin-2-yl)sulfonyl)amino)benzoic acid methyl ester], plus the acid cloransulam, calculated as parent ester	
METABOLIC PROFILE IN ANIMALS (goat, hen)		Similar	
FAT SOLUBLE RESIDUE		No	
DIETARY RISK FROM FOOD AND WATER			
Chronic non-cancer dietary risk ADI = 0.05 mg/kg bw/d EEC = 0.003025 mg a.i./L	**POPULATION**	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food	**Food + Water (EEC)**
	All infants <1 yr old	0	0.4
	Children 1 to 2 yrs	0	0.2
	Children 3 to 5 yrs	0	0.2
	Children 6 to 12 yrs	0	0.1
	Youth 13 to 19 yrs	0	0.1
	Adults 20 to 49 yrs	0	0.1
	Adults 50+ yrs	0	0.1
	Females 13 to 49 yrs	0	0.1
	Total population	0	0.1

Table 5 Differences Between Canadian MRLs and Other Jurisdictions

Commodity	Canada (ppm)	United States (ppm)	Codex* (ppm)
Soybean, forage	NA	0.1	Not reviewed by Codex
Soybean, hay	NA	0.2	
Dry soybean	0.01	0.02	

* Codex is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

None of the proposed Canadian MRLs are the same as those in the United States (http://www.access.gpo.gov/nara/cfr/ waisidx_04/40cfr180_04.html).

Under the North American Free Trade Agreement (NAFTA), Canada, the United States and Mexico are committed to resolving MRL discrepancies to the broadest extent possible. Harmonization will standardize the protection of human health across North America and promote the free trade of safe food products. Until harmonization is achieved, the Canadian MRLs proposed in this regulatory amendment are necessary. The differences in MRLs outlined above are not expected to impact businesses negatively or adversely affect international competitiveness of Canadian firms or to negatively affect any regions of Canada.

Table 6 Fate and Behaviour in the Terrestrial Environment

Property	Test Material	Value	Comments
Abiotic Transformation			
Hydrolysis	XDE-565	Half-lives pH 5 > 365 days pH 7 = 231 days pH 9 = 3 days	Not a principal route at acidic and neutral pH: parent compound rapidly transforms at basic pH
Phototransformation on soil	XDE-565	Half-life = 30–70 days	Not a principal route of transformation
Phototransformation in air	Study not submitted	—	Not expected to volatilize from water or moist soil
Biotransformation			
Biotransformation in aerobic soil	XDE-565	Half-life = 14–22 days	Slightly persistent

Property	Test Material	Value	Comments
Mobility			
Adsorption/desorption	XDE-565 XDE-565-acid	Values from batch equilibrium study K_{oc} parent = 15.8–87.1 K_{oc} XDE-565-acid = 57.0–135.3	High potential for mobility of the parent and transformation products
Volatilization	XDE-565 (from soil)	—	CO_2 was the only volatile product
Field Studies			
Field dissipation		DT_{50} < 1 wk	Non-persistent

Table 7 Fate and Behaviour in the Aquatic Environment

Property	Test Material	Value	Comments
Abiotic Transformation			
Hydrolysis	XDE-565	DT50 pH 5 > 365 days pH 7 = 231 days pH 9 = 3 days	Not a principal route at acidic and neutral pH: parent compound rapidly transforms at basic pH
Phototransformation in water	XDE-565	Half-life = 22 minutes	A principal route of transformation
Biotransformation			
Biotransformation in aerobic water systems at 20–30°C	XDE-565	Half-life = 25.6 days (in water)	Slightly persistent in water
Biotransformation in anaerobic water systems at 20–30°C	XDE-565	Half-life = 16 days in water	Slightly persistent
Biotransformation in anaerobic water systems at 5°C	XDE-565	Half-life = 237 days in water	Persistent at low temperature
Partitioning			
Adsorption/desorption	XDE-565 XDE-565-acid	K_{oc} values for adsorption ranged from 15.8 to 87.1 for XDE-565 and from 57.0 to 135.3 for XDE-565-acid.	Will remain primarily in aqueous phase

Property	Test Material	Value	Comments
Field Studies			
Field dissipation	Study not submitted	—	—

Table 8 Toxicity to Non-Target Terrestrial Organisms

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity
Invertebrates				
Earthworm	Acute	XDE-565	14-d LC_{50} > 859 mg a.i./kg soil 14-d NOEC = 116 mg a.i./kg soil	N/A
Bee	Oral	Not submitted	—	—
	Contact	XDE-565	48-h LD_{50} > 25µg a.i./bee 48-h NOEC = 3.1 µg a.i./bee	Relatively non-toxic
Birds				
Bobwhite quail	Acute	XDE-565	14-d LD_{50} > 2250 mg a.i./kg bw 14-d NOEC = 2250 mg a.i./kg bw	Practically non-toxic
	Dietary	XDE-565	8-d LC_{50} > 5620 mg a.i./kg diet 8-d NOEC = 5620 mg a.i./kg diet	Practically non-toxic
	Reproduction	XDE-565	NOEC egg reproduction/quality = 500 mg a.i./kg diet	N/A
Mallard duck	Dietary	XDE-565	8-d LC_{50} > 5620 mg a.i./kg diet 8-d NOEC = 5620 mg a.i./kg diet	Practically non-toxic
	Reproduction	XDE-565	NOEC eggshell thickness = 125 mg a.i./kg diet	N/A
Mammals				
Rat	Acute oral	XDE-565	LD_{50} > 5000 mg a.i./kg bw	Low toxicity
	Acute oral	NAF-75	LD_{50} > 5000 mg a.i./kg bw	Low toxicity

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity
	Reproductive/ developmental toxicity	XDE-565	Reproductive toxicity NOAEL = 500 mg a.i./kg bw/d	—
Mouse	90-d dietary	XDE-565	NOAEL male = 50 mg kg bw/d	—
Vascular plants				
Vascular plant	Postemergence (vegetative vigour—shoot length)	XDE-565	EC_{25} = 0.099 g a.i./ha NOEC = 0.025 g a.i./ha	N/A

Table 9 Toxicity to Non-Target Aquatic Organisms

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity
Freshwater species				
Daphnia magna	Acute	XDE-565	48-h LC_{50} = 97.5 mg a.i./L 48-h NOEC = 64.3 mg a.i./L	Slightly toxic
	Chronic	XDE-565	NOEC progeny per adult = 11.3 mg a.i./L	N/A
Rainbow trout	Acute	XDE-565	96-h LC_{50} > 86 mg a.i./L 96-h NOEC = 86 mg a.i./L	Slightly toxic
Bluegill sunfish	Acute	XDE-565	96-h LC_{50} >154 mg a.i./L 96-h NOEC = 154 mg a.i./L	Practically non-toxic

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity
Freshwater alga diatom	Acute	XDE-565	5-d EC_{25} = 1.10 mg a.i./L 5-d EC_{50} = 1.79 mg a.i./L 5-d NOEC < 0.43 mg a.i./L	N/A
Blue-green			5-d EC_{25} = 7.3 µg a.i./L 5-d EC_{50} = 12.4 µg a.i./L 5-d NOEC < 5.64 µg a.i./L	N/A
Green			5-d EC_{50} = 2.7 µg a.i./L 5-d NOEC = 0.9 µg a.i./L	N/A
Vascular plant	Dissolved in test medium	XDE-565	14-d EC_{25} = 0.91 µg a.i./L 14-d EC_{50} = 2.91 µg a.i./L 14-d NOEC frond no./plant growth = 0.78 µg a.i./L	N/A
Marine Species				
Crustacean (grass shrimp)	Acute	XDE-565	96-h LC_{50} > 121 mg a.i./L 96-h NOEC = 121 mg a.i./L	Practically non-toxic
Mollusk (oyster)	Acute	XDE-565	96-h EC_{50} = 111 mg a.i./L 96-h NOEC = 111 mg a.i./L	Practically non-toxic
Fish (silverside)	Acute	XDE-565	96-h LC_{50} > 121 mg a.i./L 96-h NOEC = 121 mg a.i./L	Practically non-toxic
Marine alga	Acute	XDE-565	5-d EC25 = 1.64 mg a.i./L 5-d EC50 = 3.55 mg a.i./L 5-d NOEC = 0.44 mg a.i./L	N/A

Table 10 Screening Level Risk Assessment on Non-Target Species Risk to Terrestrial Organisms

Organism	Exposure	Endpoint Value	EEC	RQ
Invertebrates				
Earthworm	Acute	14-d NOEC = 116 mg a.i./kg soil	0.016 mg a.i./kg	1.38×10^{-4}
Bee	Contact	LD_{50} > 25 µg a.i./ha	35 mg a.i./ha	1.25×10^{-3}
Birds				
Bobwhite quail	Acute	14 d-NOEC = 2250 mg a.i./kg bw	6.13 mg a.i./kg dw	4.16×10^{3} days equivalent dose administered to reach NOEC in laboratory population
	Dietary	8-d NOEC = 6520 mg a.i./kg diet	6.13 mg a.i./kg dw	1.09×10^{-3}
Mallard duck	Reproduction	NOEC eggshell thickness = 125 mg a.i./kg diet	1.18 mg a.i./kg dw	9.44×10^{-3}
Mammals				
Rat	Acute	LD_{50} > 5000 mg/kg bw	17.66 mg a.i./kg dw	$>5.66 \times 10^{3}$ days of daily intake to reach equivalent to kill 50% of the laboratory population
Mouse	Dietary	90-d NOAEL = 50 mg/kg bw/d	17.55 mg a.i./kg dw	3.51×10^{-1}
Vascular Plants				
Vascular plant	Postemergent	EC_{25} = 0.09 g a.i./ha	35 g a.i./ha	388.8

Table 11 Screening Level Risk Assessment on Non-Target Species Risk to Aquatic Organisms

Organism	Exposure	Endpoint Value	EEC	RQ
Freshwater Species				
Daphnia magna	Acute	48-h NOEC = 63.3 mg a.i./L	0.012 mg a.i./L	1.9×10^{-4}
Rainbow trout	Acute	96-h NOEC = 86 mg a.i./L	0.012 mg a.i./L	1.4×10^{-4}
Freshwater alga	Acute	96-h NOEC = 0.9 µg a.i./L	0.012 mg a.i./L	**13.3**
Vascular plant	Dissolved	14-d NOEC = 0.78 µg a.i./L	0.012 mg a.i./L	**15.3**

References

A. LIST OF STUDIES/INFORMATION SUBMITTED BY REGISTRANT

3.0 Impact on Human and Animal Health

PMRA 961853 1993, XDE 565: 13-Week Dietary Toxicity, 4-Week Recovery, and 13-Week Neurotoxicity Studies in Fischer 344 Rats (Neurotoxicity portion). DACO: 4.3.1

PMRA 961854 1992, XDE-565: 13-Week Dietary Toxicity Study in Beagle Dogs ., DACO: 4.3.1

PMRA 961855 2004, Validation Report for Method GRM 04.12. Determination of Residues of Cloransulam methyl and its Acid Metabolite, Cloransulam, in Whole Fish by High Performance Liquid Chromatography with Tandom Mass Spectromatic Detection.

PMRA 961859 1994, XDE 565: 13-Week Dietary Toxicity, 4- Week Recovery, and 13-Week Neurotoxicity Studies in Fischer 344 Rats (Dietary and recovery portion). Part 1, DACO: 4.3.1

PMRA 961865 1994, XDE 565: 13-Week Dietary Toxicity, 4- Week Recovery, and 13-Week Neurotoxicity Studies in Fischer 344 Rats (Dietary and recovery portion). Part 2, DACO: 4.3.1

4.0 Impact on the Environment

PMRA 961856 Description of the Persistence and Mobility Characteristics of Cloransulam and the Major Soil Transformation Products in Soil.

PMRA 961857 Effect of Soil Conditions on the Degradation of Cloransulam-methyl. J. Environ. Qual. Vol.39, may-June 2000.

PMRA 961858 Products and Kinetics of Cloransulam-methyl Aerobic Soil Metabolism. J. Agric. Food Chem. 1996, 44, 324-332.